Am. J. Trop. Med. Hyg., 90(5), 2014, pp. 882–891
doi:10.4269/ajtmh.13-0403

Review Article: Incubation Periods of Mosquito-Borne Viral Infections: A Systematic Review

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Abstract. Mosquito-borne viruses are a major public health threat, but their incubation periods are typically uncited, non-specific, and not based on data. We systematically review the published literature on six mosquito-borne viruses selected for their public health importance: chikungunya, dengue, Japanese encephalitis, Rift Valley fever, West Nile, and yellow fever viruses. For each, we identify the literature's consensus on the incubation period, evaluate the evidence for this consensus, and provide detailed estimates of the incubation period and distribution based on published experimental and observational data. We abstract original data as doubly interval-censored observations. Assuming a log-normal distribution, we estimate the median incubation period, dispersion, 25th and 75th percentiles by maximum likelihood. We include bootstrapped 95% confidence intervals for each estimate. For West Nile and yellow fever viruses, we also estimate the 5th and 95th percentiles of their incubation periods.

INTRODUCTION

Mosquito-borne viruses are a major public health threat. Dengue virus (DENV), endemic in tropical settings, has recently spread to more temperate climes, causing an estimated 50–100 million infections and 12,500 deaths per year.[1] Similarly, epidemics of West Nile virus (WNV) are a growing concern—a 2012 epidemic in the United States caused 5,674 reported cases (51% of them neuroinvasive) and 286 deaths.[2] Knowledge of the incubation period (the time between infection and the onset of symptoms) would improve 1) estimation of the timing, and hence the probable location, of infection;[3,4] 2) accurate modeling of the disease process using predictive models; and 3) evaluation of control measures (including quarantine) targeting symptomatic individuals.[5] However, the incubation periods of many mosquito-borne viruses are typically uncited, non-specific, and not based on data.[6,7] With the previously mentioned gaps in mind, we systematically reviewed the published literature on six mosquito-borne viruses selected for their public health importance: chikungunya virus (CHIKV), DENV, Japanese encephalitis virus (JEV), Rift Valley fever virus (RVFV), WNV, and yellow fever virus (YFV). For each virus, we aim to 1) identify the literature's consensus on the incubation period, 2) evaluate the evidence for this consensus, and 3) provide estimates of the incubation period that contain detail on the distribution based on published experimental and observational data.

MATERIALS AND METHODS

Search, assessment, data abstraction, and analyses largely followed the methods of Lessler and others.[6]

Search strategy and selection criteria. Searches were conducted using PubMed, Google Scholar, and ISI Web of Knowledge 4.0 as described in Lessler and others.[6] Searches were conducted between April 15, 2010 and January 6, 2011, with no restrictions on the earliest date of the articles returned. Each search was done with common variations of the virus name, specifically: Japanese encephalitis, Japanese B Encephalitis, JE, JEV, JBE, West Nile, WN, WNV, Rift Valley fever, RVF, RVFV, chikungunya, CHIK, CHIKV, dengue, DEN, DENV, yellow fever, YF, and YFV. We also reviewed the infectious disease reference, Field's Virology, several library catalogues, and the Cochrane Library.

Two reviewers independently reviewed and categorized abstracts. Abstracts summarizing a study of human infection of one of the six mosquito-borne viruses included in this review were designated for full-text review. The reviewers resolved discrepancies through discussion and consensus. This review satisfies the PRISMA and QUORUM systematic review checklists.

Assessment. Assessment was performed on documents included in the full-text review as described in Lessler and others.[6] Documents were classified as either containing a statement of the incubation period or not. Those containing an incubation period statement were further classified according to whether the statement was 1) based on and ascertainable from original data, 2) based on but not ascertainable from original data, 3) sourced, or 4) unsourced. Those not containing an incubation period statement were further classified according to whether the article 1) contained original data that could be used to ascertain an incubation period, 2) contained original data that could not be used to ascertain an incubation period, or 3) did not contain any original data.

Two reviewers abstracted incubation period statements and original incubation period data as described in Lessler and others.[6] We report the incubation period range consistent with over 50% of the abstracted statements.

Pooled analysis. As in Lessler and others,[6] original data that could be used to ascertain an incubation period were abstracted as doubly interval-censored observations. Assuming a log-normal distribution, incubation period quantiles and a dispersion parameter were estimated for each virus by maximum-likelihood using the coarseDataTools package for R.[8] We used 500 bootstrapped samples to calculate 95% confidence intervals (CIs). For each of DENV, WNV, and YFV, pooled data were analyzed 1) including only those who were infected by a mosquito, and 2) including all abstracted cases. For each of CHIKV, JEV, and RVFV, pooled data were analyzed including all abstracted cases, because there were not enough mosquito-infection observations to perform separate analyses. Cases of maternal-child transmission were excluded from the analyses. We

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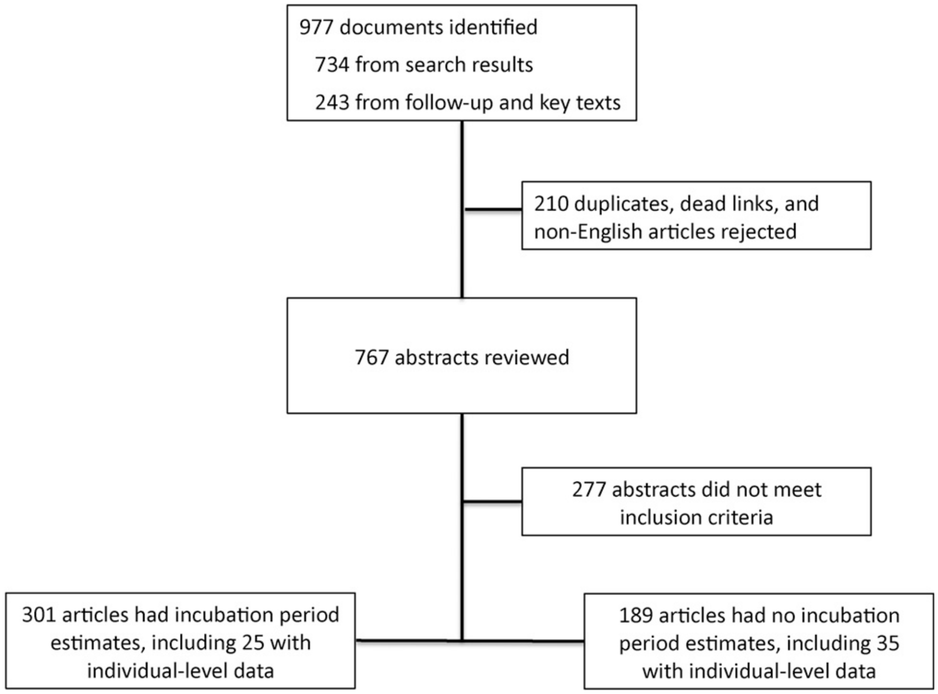

FIGURE 1. Systematic review process.

conducted a separate analysis of cases infected by WNV through blood transfusion or surgery. All analyses were done using the R statistical package (version 2.14.1). All data and a complete bibliography are available from the authors upon request.

RESULTS

We identified 977 articles containing incubation period statements (Figure 1). Table 1 summarizes the incubation periods stated in the literature for each virus. Of the 375 estimates included in these articles, 34 (9%) were original, 129 (34%) were not original but provided a source, and 212 (57%) were not original and did not provide a source. Table 2 summarizes the 60 articles containing individual-level data appropriate for pooled analysis (Table 2). Estimates for the incubation period of YFV and DENV had the most support (14 studies and 19 studies, respectively). Fewer than 25 observations were available for each of CHIKV, RVFV, and WNV; and only 6 observations were available for JEV.

Estimates of the full distribution of each incubation period using pooled data are shown in Figure 2 and Table 3. To characterize the distribution, we provide the incubation periods within which 25%, 50%, and 75% of cases become symptomatic. Where possible, we provide incubation period estimates for the subset of mosquito-acquired infections. We also provide the 5th and 95th percentile incubation period estimates for WNV (all observations) and YFV (all observations and the mosquito-acquired subset). There were insufficient data to confidently estimate the 5th or 95th incubation period percentiles for CHIKV, DENV, JEV, and RVFV. Median incubation periods ranged from 2.6 days (for WNV) to 8.4 days (for JEV). Dispersions ranged from 1.04 to 1.82.

Chikungunya virus. The CHIKV is a mosquito-borne virus first discovered in Tanzania in the early 1950s, and it causes an illness characterized by fever and joint pain.[70] Historically, infection rates were low and limited to regions in Africa and Asia.[71] However, a recent mutation may have increased the virus' preference for the *Aedes (Ae.) albopictus* mosquito.[72,73] *Aedes albopictus* is thought to have been a major vector in

TABLE 1
Summary of incubation period estimates in the published literature

Disease	Literature estimates (days): Range	Literature estimates (days): Central tendency	Number of estimates (%): Unsourced estimates	Number of estimates (%): Sourced estimates	Number of estimates (%): Original estimates [experimental/ observational]	Participants in experimental studies
CHIKV	2–10	3	21 (60%)	12 (34%)	2 [0/2]	N/A
DENV	3–10	4	66 (49%)	56 (41%)	13 [8/5]	128
JEV	5–15	7*	25 (69%)	9 (25%)	2 [0/2]	N/A
RVFV	3–6	3–4†	10 (59%)	3 (18%)	4 [0/4]	1
WNV	3–14	4‡	51 (58%)	32 (36%)	5 [1/4]	8
YFV	3–6	6	39 (61%)	17 (27%)	8 [1/7]	25

*Only one point estimate consistent with the literature, "about a week."[9]
†One point estimate, "The illness was characterized by an incubation period of 4 days"[10]; and one point estimate, "developed virologically proven RVF 3 days later."[11]
‡Only one point estimate, "about 4 days."[12]

Table 2
Details of works that included individual-level data for inclusion in the pooled analysis*

	Location	Study type	*N*	Population	Infection mechanism
CHIKV					
ICDDR, 2009[13]	Bangladesh	Observational	2	Male in 30s, 36-year-old female	Mosquito
CDC, 2006[14]	Zimbabwe	Observational	1	Adult male	Mosquito
Parola and others, 2006[15]	Indian Ocean Islands	Observational	1	60-year-old female	Direct contact with blood
Beltrame and others, 2007[16]	Italy	Observational	13	4 females ages 36–57, 9 males ages 31–66	Mosquito
Receveur and others, 2010[17]	Maldives Islands (Indian Ocean)	Observational	1	Male in 30s	Mosquito
Tang, 2006[18]	Mauritius (Indian Ocean)	Observational	1	66-year-old male	Mosquito
Soon and others, 2007[19]	Southern Indian	Observational	1	49-year-old female	Mosquito
Volpe and others, 2006[20]	Reunion Island	Observational	1	46-year-old female	Mosquito
DENV					
Ashburn and others, 1907[21]	Philippines	Experimental	10	Adult males	Injection
Bancroft, 1906[22]	Australia	Experimental	2	Males ages 29, 34	Mosquito
Cleland and others, 1919[23]	Australia	Experimental	11	28-year-old female; 10 males ages 25–76	Injection
Yeo and others, 2005[24]	Vietnam	Observational	1	25-year-old male	Mosquito
Cleland and others, 1918[25]	Australia	Experimental	17	27-year-old female; 16 males ages 18–56	injection
Ito and others, 2007[26]	Japan	Observational	22	Not reported	Mosquito
Senanayake, 2006[27]	Australia	Observational	1	Female in 30s	Mosquito
Courtney and others, 2009[28]	Guatemala	Observational	1	15-year-old male	Mosquito
Hanna and others, 2003[29]	Australia	Observational	1	Adult male	Mosquito
Hill, 1992[30]	Haiti	Observational	1	31-year-old female	Mosquito
Graham, 1903[31]	Lebanon	Experimental; Observational	8	7 adult males; 1 adult female	Mosquito
Siler and others, 1926[32]	Philippines	Experimental	47	Adult males	Mosquito
Simmons and others, 1931[33]	Philippines	Experimental	24	Adult males	Mosquito; Injection
Schule, 1928[34]	Philippines	Experimental	9	Males ages 18–27	Mosquito
Chandler and others, 1923[35]	United States	Observational	6	4 males ages 20–30; 2 females ages 19,31	Mosquito; Injection
Hare, 1898[36]	Australia	Observational	2	Adults	Mosquito
Koizumi and others, 1918[37]	Taiwan	Observational; Experimental	2	Adults	Mosquito
Agramonte, 1906[38]	Cuba	Observational	2	Adolescent males	Mosquito
Vassal and others, 1909[39]	Boat in Indian Ocean	Observational	2	Males	Mosquito
JEV					
Buhl and others, 1996[40]	Denmark	Observational	1	51-year-old male	Mosquito
Caramello and others, 2007[41]	Italy	Observational	1	49-year-old male	Mosquito
Lehtinen and others, 2008[42]	Finland	Observational	1	60-year-old male	Mosquito
MacDonald and others, 1989[43]	Australia	Observational	1	10-year-old female	Mosquito
Ostlund and others, 2004[44]	Sweden	Observational	1	80-year-old male	Mosquito
Wittesjo and others, 1995[45]	Sweden	Observational	1	60-year-old female	Mosquito
RVFV					
Daubney and others, 1931[46]	Kenya	Experimental	1	Adult male	Inoculation
Findlay, 1932[47]	UK	Observational	3	Adult males	Contact with infected animal tissue
Francis and others, 1935[48]	USA	Observational	1	22-year-old male	Aerosol when cleaning laboratory
Hoogstraal and others, 1979[11]	Egypt	Observational	6	Adults	Contact with infected animal tissue
Kitchen, 1934[49]	USA	Observational	2	Males ages 24, 37	Laboratory infection
Mundel and others, 1951[10]	South Africa	Observational	6	Males ages 32–64	Contact with infected animal tissue
Sabin and others, 1947[50]	USA	Observational	1	Adult male	Laboratory infection
Smithburn and others, 1949[51]	Uganda	Observational	3	Males ages 22–25	Laboratory infection
WNV					
Campbell and others, 2002[52]	USA	Observational	2	Adults	Laboratory infection
Kokernot and others, 1959[12]	South Africa	Observational	1	26-year-old male	Mosquito
Nash and others, 2001[53]	Airplane	Observational	1	Adult	Mosquito
Olejnik, 1952[54]	Israel	Observational	6	Adults and children	Mosquito
Southam and others, 1954[55]	USA	Experimental	8	Males and females ages 23–73	Inoculation
YFV					
Hindle, 1930[56]	United States	Observational	2	Adult males	Direct contact with blood
Colebunders and others, 2002[57]	The Gambia	Observational	1	47-year-old female	Mosquito

(continued)

TABLE 2
Continued

	Location	Study type	N	Population	Infection mechanism
Smith and others, 1968[58]	Cuba	Observational	31	Males and females, ages 6–60	Mosquito
McFarland and others, 1997[59]	Brazil	Observational	1	45-year-old male	Mosquito
CDC, 2000[60]	Venezuela	Observational	1	48-year-old male	Mosquito
Low and others, 1931[61]	London	Observational	1	28-year-old male	Laboratory infection
Carter, 1901[62]	USA	Observational	18	16 males, 2 females	Mosquito
Reed, 1902[63]	Cuba	Experimental	25	Not reported	Mosquito; injection
Berry and others, 1931[64]	USA	Observational	2	Males ages 35, 24	Laboratory infection
Bugher and others, 1944[65]	Columbia	Observational	1	Male	Mosquito
Dudley, 1933[66]	Sierra Leone	Observational	4	Adult males	Mosquito
WHO, 2000[67]	Venezuela	Observational	1	48-year-old male	Mosquito
CDC, 2002[68]	Brazil	Observational	1	47-year-old male	Mosquito
Nolla-Salas and others, 1989[69]	West Africa	Observational	1	37-year-old female	Mosquito

*CHIKV = chikungunya virus; DENV = dengue virus; JEV = Japanese encephalitis virus; YFAV = yellow fever virus.

recent outbreaks in India, several countries in the Indian Ocean,[74] and the first European outbreak in Northern Italy in 2007.[75] The continued spread of *Ae. albopictus* across Europe and the Americas heightens the potential public health impact of the virus, for which there is no vaccine.[71,76]

We found 32 documents with statements of the incubation period for CHIKV that provided two original estimates, 12 sourced estimates, and 21 unsourced estimates. (Three documents provided two estimates each.) Both of the original estimates were from observational studies. Only five of the sourced estimates were from primary sources. Several of these came from the original report of CHIKV—a 1955 publication of the 1952–1953 epidemic in Zanzibar.[77] The author of this report estimated the incubation period of CHIKV from several hospital patients who had a single contact with an infectious village. Most estimates are consistent with an incubation period of 2–12 days (Table 1).

We extracted a total of 21 observations of the incubation period from eight observational studies. We estimated a median incubation period of 3.0 days (95% CI: 0.5–3.1) with a dispersion of 1.04 (95% CI: 1.04–1.08).

The study with the most observations (13) reported demographic and epidemiologic data on travelers diagnosed with chikungunya while visiting Italy between July and September 2006. Because the exact date and time of the infectious mosquito bite could not be identified, the incubation period estimates for these travelers ranged from < 1 day to a maximum of 31 days.[16] We also found two articles reporting vertical transmission, but these cases were excluded from the analysis.[78,79] One of these reports involved 19 infants born to 61 infected mothers on La Reunion Island over a 22-month period.[78] The median time from delivery to when the infants presented symptoms was 4 days with a range of 3–7 days. The other report of vertical transmission was also from La Reunion Island, included six infants, and estimated the incubation period range to be 3–5 days.[79]

Dengue virus. The DENV is a mosquito-borne virus with four distinct serotypes that cause a flu-like illness, fever, and sometimes a more severe complication called dengue hemorrhagic fever. The DENV is endemic to over 100 countries, and, according to the World Health Organization (WHO), ~2/5 of the world's population are now at risk.[1] The DENV is transmitted by *Ae.* mosquitoes, primarily by *Ae. aegypti* and secondarily by *Ae. albopictus*. Both mosquito species have geographically spread in recent years—*Ae. aegypti* particularly in urban areas and *Ae. albopictus* particularly in temperate regions (e.g., the southern portion of the United States).[76] Several vaccine candidates are currently under study.[1,80]

We found 100 papers that provided a total of 135 incubation period estimates for DENV. (Several papers provided multiple and/or a combination of sourced, unsourced, and original estimates.) Of these estimates, 13 were based on original data and 56 were sourced. The most commonly referenced primary source was a book chapter by military officer J. F. Siler and others, which reported an experiment performed on 47 patients in 1924 in the Philippines.[32] More recent case definitions included serologic confirmation, but those extracted from studies published in the late 19th and early 20th centuries were based primarily on clinical symptoms and history of exposure. Most estimates are consistent with an incubation period of 3–14 days (Table 1).

We extracted a total of 169 individual-level observations of the incubation period, including 128 observations from experimental studies. Based on these 169 observations, we estimate the median incubation period for DENV to be 5.6 days (95% CI: 5.3–6.0) with a dispersion of 1.41 days (95% CI: 1.34–1.50) (Table 3). Twenty-five percent of cases developed symptoms by 4.5 days following infection (95% CI: 4.1–4.9), and 75% developed symptoms by 7.1 days (95% CI: 6.7–7.6). There were insufficient data to confidently estimate the 5th or 95th percentiles. Restricting the analysis to the 124 individual-level observations from mosquito-transmitted infections, including 85 observations from experimental studies, we estimated a median incubation period of 5.3 days (95% CI: 5.0–5.7) with a dispersion of 1.37 (95% CI: 1.27–1.52). These estimates agree with a recent paper in which the authors completed a systematic review of the intrinsic incubation period of DENV.[81] Based on 204 observations from 35 studies, they estimated a mean incubation period of 5.9 days and 95% of cases developed symptoms between 3.4 and 10 days.

Japanese encephalitis virus. The JEV is a mosquito-borne virus, amplified in pigs and birds, and found throughout Asia and parts of Australia.[82–84] The JEV is reported to be responsible for 50,000 cases and 10,000 deaths annually,[85,86] but up-to-date estimates are lacking, possibly caused by the absence of encephalitis surveillance systems in several affected Asian countries.[87] Before the introduction of

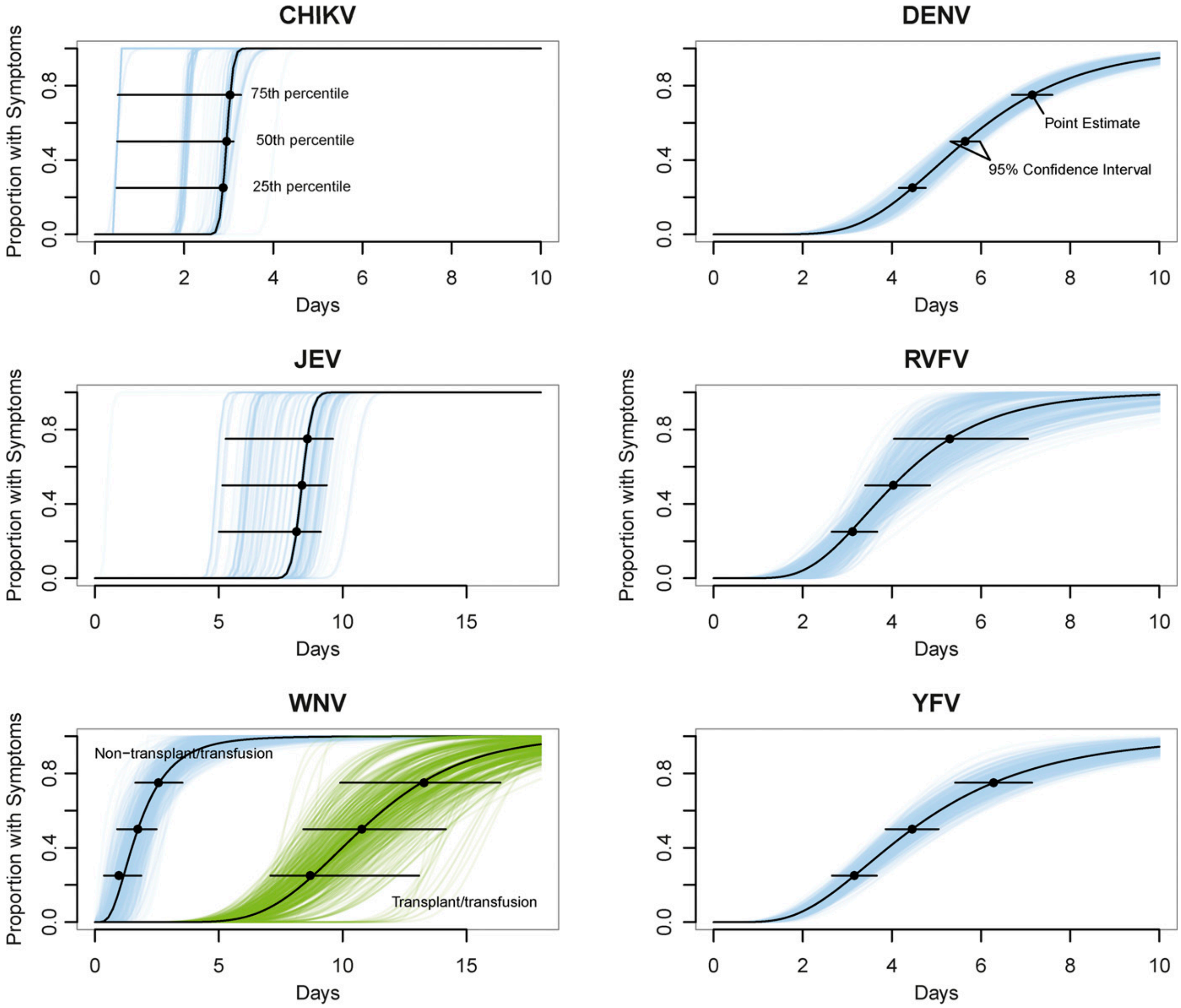

FIGURE 2. Estimated cumulative distributions of the incubation periods. Horizontal bars show the 95% confidence intervals at the 25th, 50th, and 75th percentiles. Individual lines represent bootstrap samples.

vaccination, nearly all children in endemic countries were infected, but infections were usually asymptomatic.[88]

We found 35 documents with statements of the incubation period for JEV that provided two original estimates, nine sourced estimates, and 25 unsourced estimates. Of the two original estimates, both derived from observational studies. One of the sourced estimates was a report of an elderly Swedish tourist who acquired Japanese encephalitis

TABLE 3
Percentiles of the time of symptom onset and dispersion for incubation period distributions

Virus	Estimate (95% CI) of time of symptom onset (days)*					
	5th	25th	50th	75th	95th	Dispersion (95% CI)
CHIKV	N/A	2.9 (0.5, 3.0)	3.0 (0.5, 3.1)	3.0 (0.5, 3.3)	N/A	1.04 (1.04, 1.08)
DENV	N/A	4.5 (4.1, 4.9)	5.6 (5.3, 6.0)	7.1 (6.7, 7.6)	N/A	1.41 (1.34, 1.50)
DENV mosquito only	N/A	4.3 (3.8, 4.7)	5.3 (5.0, 5.7)	6.6 (6.2, 7.2)	N/A	1.37 (1.27, 1.52)
JEV	N/A	8.1 (5.0, 9.1)	8.4 (5.1, 9.4)	8.6 (5.3, 9.6)	N/A	1.04 (1.04, 1.05)
RVFV	N/A	3.1 (2.7, 3.7)	4.0 (3.4, 4.9)	5.3 (4.0, 7.1)	N/A	1.50 (1.22, 1.82)
WNV	1.0 (0.4, 1.9)	1.7 (0.9, 2.5)	2.6 (1.6, 3.5)	3.8 (2.5, 5.6)	7.0 (3.6, 12.4)	1.82 (1.27, 2.67)
WNV mosquito only	N/A	2.8 (0.4, 3.0)	2.9 (0.5, 3.1)	3.0 (0.6, 3.2)	N/A	1.04 (1.04, 1.29)
WNV transplant only	N/A	8.7 (7.1, 13.1)	10.8 (8.4, 14.2)	13.3 (9.9, 16.4)	N/A	1.35 (1.12, 1.47)
YFV	1.9 (1.7, 2.3)	3.2 (2.8, 3.5)	4.4 (4.0, 5.0)	6.3 (5.3, 7.3)	10.3 (7.9, 12.8)	1.66 (1.48, 1.82)
YFV mosquito only	1.9 (1.6, 2.3)	3.1 (2.8, 3.5)	4.4 (3.9, 5.0)	6.2 (5.1, 7.4)	10.3 (7.5, 13.1)	1.67 (1.47, 1.84)

*CHIKV = chikungunya virus; DENV = dengue virus; JEV = Japanese encephalitis virus; RVFV = Rift Valley fever virus; WNV = West Nile virus; YFV = yellow fever virus.

while traveling in Java and Bali.[44] The patient developed encephalitis after a reported incubation period of up to 17 days, but it is plausible that infection could have occurred at any point during the 3-week visit, resulting in an incubation period between four and 26 days. In addition to this case, we found only five other documents containing data with ascertainable incubation periods ranging from 0 to 23 days. All were case reports of infected tourists.

We only found data on six individual ascertainable incubation periods. Using these limited data, we estimate that JEV has a median incubation period of 8.4 days (95% CI: 5.1–9.4). This is similar to the central tendency of 7 days reported in the literature and falls within the 5–15 days incubation period often referenced (Table 1).[9]

Rift Valley fever virus. The Rift Valley fever is largely a disease of livestock. However, it bears medical importance, as RVFV spreads to humans during livestock outbreaks by direct contact and mosquito transmission.[89] For example, there were ~200,000 human cases during a livestock outbreak in Egypt in 1977–78.[90] Despite the disease's deadly effect on livestock, it typically presents as a mild, influenza-like illness in humans. However, life-threatening complications, including hemorrhagic fever and encephalitis, develop in about 1% of cases.[91] This is a non-trivial number in large outbreaks—during the 1977–78 Egyptian outbreak, there were an estimated 600 deaths.[90] The RVFV has been confined to the African continent until recently when outbreaks were confirmed in both Saudi Arabia and Yemen.[92]

We found 16 documents with statements of the incubation period for RVFV that provided four original estimates, three sourced estimates, and 10 unsourced estimates. Of the four original estimates, all derived from observational studies. The observational study with the most data came from a 1951 report of the incubation period in several South African veterinarians and farmhands who handled the organs of a bull infected with RVFV.[10] Estimates are consistent with an incubation period of 3–6 days (Table 1).

Based on 23 observations from one experimental and seven observational studies, we estimate the median incubation period for RVFV to be 4.0 days (95% CI: 3.4–4.9), with a dispersion of 1.50 (95% CI: 1.22–1.82). Twenty-five percent of cases developed symptoms by 3.1 days (95% CI: 2.7–3.7) and 75% by 5.3 days (95% CI: 4.0–7.1) after infection. There were insufficient data to confidently estimate the 5th or 95th percentiles. However, it is important to note that at least 17 of these 18 observations were not transmitted by mosquitoes. Most were laboratory infections or infections following the butchering or postmortem examination of deceased, infected livestock. The sole experimental incubation period data came from the first published paper on the disease. Veterinary investigators of an outbreak among sheep on a farm in the Kenyan Rift Valley inoculated a hospitalized adult male with the virus and reported an incubation period of about 3 days.[46,91]

West Nile virus. The geographic distribution of WNV is nearly global after rapidly expanding over the past two decades to include the United States, Canada, Mexico, the Caribbean, and portions of South America.[86,93] The first documented outbreak in the Western Hemisphere was in New York City in 1999 and incurred 59 hospitalized cases and seven deaths.[53–95] In endemic regions, WNV typically manifests as a mild or dengue-like illness,[96] but among more recently exposed populations, neuroinvasive symptoms (e.g., meningitis, meningoencephalitis, and encephalitis) may be more common.[52,97] For instance, in Queens, during the 1999 New York City outbreak, there was one meningoencephalitis case estimated for every 140 infections.[98]

We found 76 documents with statements of the incubation period for WNV that provided five original estimates, 32 sourced estimates, and 51 unsourced estimates. Of the five original estimates, one derived from an experimental study and four derived from observational studies. The experimental study, published in 1952, involved inoculating advance-stage cancer patients with WNV.[55] A related experiment by the same authors contributed individual-level data and is discussed below. One of the observational studies with the most data was reported by researchers in Israel in 1952. During an outbreak of WNV in the Kibbutz Mayan Tsevi, the group of researchers were able to estimate the incubation period from individuals' movements into and out of the kibbutz.[54] Incubation period estimates for WNV are consistent with an interval of 3–14 days (Table 1).

In 2002, four organ transplant patients in the Southeastern region of the United States were infected with WNV through a common donor[99]; this was the first documented instance of WNV transmission through organ transplantation. After incubation periods ranging from 6 to 18 days, three of the four transplant recipients developed encephalitis—two required mechanical ventilation support and one died. Our review returned individual-level data from which incubation periods could be estimated for five transplant patients and one blood transfusion patient. For these six patients, the median incubation period was 10.8 days with an interquartile range of 8.4–14.2 days.

Based on 18 observations from one experimental and four observational studies, we estimate the median incubation period for WNV to be 2.6 days (95% CI: 1.6–3.5), with a dispersion of 1.82 (95% CI: 1.27–2.67). Twenty-five percent of cases develop symptoms by 1.7 days (95% CI: 0.9–2.5) and 75% by 3.8 days (95% CI: 2.5–5.6) after infection. Five percent of cases develop symptoms by 1.0 day (95% CI: 0.4–1.9) and 95% by 7.0 days (95% CI: 3.6–12.4) after infection.

Of these 18 observations, eight were likely mosquito transmitted. We estimate the median incubation period for mosquito-transmitted WNV to be 2.9 days (95% CI: 0.5–3.1), with a dispersion of 1.04 (95% CI: 1.04–1.29).

Yellow fever virus. Mild manifestation of YFV is clinically indistinguishable from several of the previous viruses (e.g., RVFV, DENV).[86] Severe cases, however, develop jaundice (for which YFV is named), increased vomiting and, in 15–25% of cases, hemorrhage.[86,100] Persistent underreporting of yellow fever cases challenges estimates of the human toll,[101] however the WHO estimates 200,000 cases and 30,000 deaths annually, most of which occur in Africa and Central and South America. Vaccination is the central prevention strategy with campaigns administered effectively since the 1940s[86]; in 2008, routine immunization provided coverage to 91% of eligible adults and children in the Americas and 43% in Africa. Eight African countries that conducted targeted campaigns were able to reach over 90% of the eligible population.[102]

We found 56 documents with statements of the incubation period for YFV that provided 8 original estimates, 17 sourced estimates, and 39 unsourced estimates. Of the 8 original estimates, one derived from an experimental study and seven derived from observational studies. Most estimates are consistent with an incubation period of 3–6 days (Table 1).

Based on 91 observations from one experimental and 13 observational studies, we estimate the median incubation period for YFV to be 4.4 days (95% CI: 4.0–5.0) with a dispersion of 1.66 (95% CI: 1.48–1.82). Twenty-five percent of cases develop symptoms by 3.2 days (95% CI: 2.8–3.5) and 75% by 6.3 days (95% CI: 5.3–7.3) after infection. Five percent of yellow fever cases developed symptoms by 1.9 days (95% CI: 1.7–2.3), and 95% of cases developed symptoms by 10.3 days (95% CI: 7.9–12.8) following infection. After excluding 11 observations that were not transmitted by mosquitoes, incubation period estimates remained nearly unchanged with a median of 4.4 days (95% CI: 3.9–5.0), dispersion of 1.67 (95% CI: 1.47–1.84), 25th percentile of 3.1 days (95% CI: 2.8–3.5), and 75th percentile of 6.2 days (95% CI: 5.1–7.4).

We also found four papers reporting cases of yellow fever following vaccination, but these cases were excluded from the analysis[103–106]; three of the four reports were from the July 14, 2001 issue of the Lancet and detailed serious adverse events from vaccination with the 17D and 17DD YFV substrains. The reported incubation period for these cases ranged from 2 to 4 days.

DISCUSSION

Given the global spread of mosquito-borne viruses in recent years, knowledge of their incubation periods assumes increasing importance in efforts to identify and control epidemics. However, statements of the incubation periods are typically a weak point in the literature. In our review, we found that 57% of the 375 estimates were uncited, and of those that were cited, over half cited an unsourced estimate. In total, the 375 incubation period estimates could be traced back to a mere 32 original data sources. To address this gap, we systematically reviewed the literature and characterized the incubation periods of CHIKV, DENV, JEV, RVFV, WNV, and YFV using individual-level observations from as far back as 1898.

There are several sources of uncertainty that limit our estimates. Uncertainty in the timing of infection and illness motivated our use of doubly interval-censored data, which accounts for uncertainty in both the period of infection and period of illness onset.[8] Uncertainty in the time of infection may be further compounded as different studies may have slightly different definitions of the start of infection. To limit this source of variability, we defined onset as the time that any flu-like symptom (e.g., fever, chills) was reported. We believe our approach is conservative.

There is little published data on the incubation periods of JEV, RVFV, and CHIKV. For example, our estimates for the incubation period of JEV were only based on six studies. This lack of data is reflected in the wide confidence intervals for the median incubation period estimates and the inability to estimate the 5th and 95th percentiles of the incubation period for these viruses. Additional observational studies with details on the exposure period and illness onset are important to characterize these incubation periods with more precision. In addition, the majority of infections are not published. If these unpublished cases systematically differ from published cases, then our results may not be representative of all the infections.

Incubation periods may differ by mode of infection (e.g., mosquito, injection, aerosol, transfusion/transplant, and mother-to-child), immune status, and viral strain. We attempted to account for this effect heterogeneity where possible by estimating incubation periods separately for mosquito- and non-mosquito-transmitted infections, and separately for transplant and transfusion infections in the case of WNV. We found that incubation periods were similar between mosquito- and non-mosquito, non-transfusion-transmitted infections for DENV, WNV, and YFV. (CHIKV, RVFV, and JEV did not have enough data to make this comparison.) Incubation periods for West Nile transplant/transfusion-acquired infections were longer than for mosquito-acquired infections. However, more observational data is needed to precisely characterize the incubation periods for these subgroups and others—particularly in vulnerable subpopulations such as infants.

Despite limitations stemming from a lack of observational data, a key strength of this analysis is its compilation and use of available published data to fill a gap in the understanding of several mosquito-borne viruses and the diseases they cause. Climate change will continue to facilitate the spread of mosquito habitats. Indeed, the Asian tiger mosquito—which is capable of carrying CHIKV, DENV, WNV, and YFV[74,76,107,108] is now found as far north as the Netherlands in Europe and Minnesota in the United States.[109,110] Identification and control of mosquito-borne virus outbreaks will become increasingly important as mosquito habitats expand to previously unexposed populations. Our characterizations of these incubation periods provide a level of detail useful for outbreak prediction, management, and control efforts.

Received July 11, 2013. Accepted for publication November 14, 2013.

Published online March 17, 2014.

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